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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR    | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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PATENT LAW DEPARTMENT  
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EXAMINER

DEBERRY, REGINA M

| ART UNIT | PAPER NUMBER |
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|----------|--------------|

1647

DATE MAILED: 03/25/2002

10

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/604,938

Applicant(s)

BALION, PASCAL SEBASTIAN

Examiner

Regina M. DeBerry

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01 November 2001.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-60 is/are pending in the application.
- 4a) Of the above claim(s) 16-22 and 49-54 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-15, 23-48 and 55-60 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 1-60 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3,6.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

***Status of Application, Amendments and/or Claims***

The information disclosure statement filed 20 October 2000 (Paper No. 3) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. The information disclosure statement filed 25 January 2001 (Paper No. 6) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. They have been placed in the application file and the information referred to therein has been considered as to the merits.

The amendment filed 01 November 2001 (Paper No. 9) has been entered in full. Applicant's election with traverse of Group I in Paper No. 9 (claims 1-15, 23-48 and 55-60) is acknowledged. The traversal is on the grounds that all the pending claims include subject matter in the elected group of "erythropoietin conjugates or compositions". Applicants state that any complete search performed for conjugates of n poly(ethylene glycol) and human erythropoietin would, of necessity, turn up prior art conjugates of n poly(ethylene glycol) and human erythropoietin modified to add one or more glycosylation sites. This is found partly persuasive. The groups are drawn to patentably distinct inventions which are different physically and functionally. In addition, the fusion protein comprised the carboxy terminus sequence of a different protein and sequence. The various modifications of erythropoietin, however, will be searched. The requirement is still deemed proper and is therefore made FINAL.

Claims 16-22 and 49-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic

or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

***Matter of Record***

Please note that the claims of the instant application claim priority under 35 U.S.C. 119(e) to four different provisional applications : 60/166,151 (17 November 1999), 60/151,548 (31 August 1999), 60/150,225 (23 August 1999), and 60/142,254 (02 July 1999). However, Applicant does not disclose conjugate percentages (claims 30-48 and 55-60 of the instant application) in any of the aforementioned provisional applications. Therefore, the priority date of the claims that recite conjugate percentages of the instant application is deemed to be 27 June 2000.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 is drawn to the conjugate of claim 3, wherein the human erythropoietin glycoprotein is expressed by endogenous activation. Endogenous means originating from within the body. It is unclear how a conjugate comprising erythropoietin, which is man made, can be expressed by endogenous gene activation.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3, 6-15 and 23-29 are rejected under 35 U.S.C. 103(a) as being obvious over Kawaguchi *et al.* (US Patent No. 4,806,524, IDS#A10 Paper No. 6) in view of Bailon *et al.* (US Patent No 6,025,324, IDS#A7 Paper No. 3), Hakimi *et al.* (European Publication No. 0510356 A1, IDS#B11 Paper No. 3) and Elliott *et al.* (WO 95/05465).

The applied reference (Bailon *et al.*, US Patent No. 6,025,324) has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For

Art Unit: 1647

applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(I)(1) and § 706.02(I)(2).

Kawaguchi *et al.* teach human erythropoietin (EPO) is a circulating glycoprotein that stimulates the formation of red blood cells. Kawaguchi *et al.* teach that EPO is an instable substance which can be made stable by formulating EPO with polyethylene glycol (PEG) (column 1, lines 1-40 and Table 1). Kawaguchi *et al.* do not teach glycosylation or how polyethylene glycol is conjugated to EPO.

Bailon *et al.* teach the conjugation of PEG with a biologically active human obese protein comprising SEQ ID NO:6. Bailon *et al.* teach a conjugate (column 12, line 45; column 13, lines 32-36 and claims 4-6 and 15). Bailon *et al.* teach limitations of PEG that overlap the limitations of PEG as claimed in the instant application such as: an amide bond with an amino group and the -CO of PEG, R is lower alkyl, n is from 300 to 1500 (this equals m where m is from 450 to 900 in the instant claims) and the average molecular weight of the PEG units in the conjugates which comprises the composition is from 35 to 45 kilo Dalton.

Hakimi *et al.* also teach the conjugation of PEG with a protein (page 2, lines 30-45; page 3, line 35 structure I-E and line 40-46). The PEG conjugate overlaps the limitations of PEG claimed in the instant application such as R1 can be any lower alkyl preferably methyl (page 4, lines 45-48). Most importantly, Hakimi *et al.* teach the use of

Art Unit: 1647

unique linkers which connect free amino groups in a protein to PEG which circumvent the problems associated in the conjugates of a protein with PEG (page 2, lines 7-29).

Elliott *et al.* (WO 95/05465) teach EPO analogs having at least one additional site for glycosylation, or a rearrangement of at least one site for glycosylation. Elliott *et al.* teach human EPO modifications by the addition of from 1 to 6 glycosylation sites. Elliott *et al.* teach carbohydrate attachments of asparagine residues (N-linked) at positions 30, 51, 57, 69, 88, 89, 136 and 138 in the human EPO amino acid sequence (page 15, lines 16-33 and page 56, Table 6). Elliott *et al.* teach addition N-linked carbohydrate chains at position 30 and 88 of the human EPO sequence (page 18, lines 4-10). Elliott *et al.* teach Asn30Thr32Val87Asn88Thr90EPO 9 (page 44, Table 3; page 48, lines 5-6; page 49, lines 26-30 and page 56 Table 6).

It would be obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings Kawaguchi regarding the stability of EPO linked to PEG, by using the PEG conjugate and the teachings of how to conjugate PEG to a protein by Bailon and Hakimi and the glycosylation taught by Elliott. The motivation and expectation of success is provided by the teachings of Kawachi regarding the stability of EPO when conjugated to PEG, the teachings of Bailon and Hakimi who to teach how to conjugate PEG to a protein and why certain bonds are more efficient and finally the teachings of Elliott who state increases in glycosylation increase the *in vivo* biological activity of EPO.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kawaguchi *et al.*, Bailon *et al.*, Hakimi *et al.* and Elliott *et al.* as applied to claims 1-3

Art Unit: 1647

and 6-15, 23-29 above, and further in view of Garvin *et al.* US Patent No. 5,641,663.

The teachings of Kawaguchi *et al.*, Bailon *et al.*, Hakimi *et al.* and Elliott *et al.* are discussed above. None of the references teach the sequence of SEQ ID NO:1. Garvin *et al.* teach the sequence of SEQ ID NO:1. Please see reference and search query (Appendix A).

It would be obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Kawaguchi *et al.*, Bailon *et al.*, Hakimi *et al.* and Elliott *et al.* by using the teachings of Garvin regarding SEQ ID NO:1. The motivation and expectation of success is provided by the teachings of Kawachi regarding the stability of EPO when conjugated to PEG, the teachings of Bailon and Hakimi who to teach how to conjugate PEG to a protein and Garvin who teach the production of biologically active EPO.

Claims 30-48 and 55-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawaguchi *et al.*, Bailon *et al.*, Hakimi *et al.* and Elliott *et al.* as applied to claims 1-3 and 6-15, 23-29 above, and further in view of Burg *et al.* US Patent No. 6,340,742 B1. The teachings of Kawaguchi *et al.*, Bailon *et al.*, Hakimi *et al.* and Elliott *et al.* are discussed above. None of the references disclose conjugate percentages. Burg *et al.* teach EPO-PEG conjugates (claims 85-89). Burg *et al.* teach EPO-PEG conjugates which overlap the percentage of conjugates in the instant application.

Art Unit: 1647

It would be obvious to one of ordinary skill in the art at the time the invention was made to substitute the PEG conjugate taught by Bailon *et al.* and Hakimi *et al.* and conjugate it with glycosylated EPO of Elliott *et al.* and use the teachings of percentage of conjugates disclosed by Burg *et al.* The motivation and expectation of success is provided by the increased circulating half-life of EPO-PEG taught by Burg.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 6-15 and 23-29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-6 and 15 of U.S. Patent No. 6,025,324 in view of Kawaguchi *et al.* (US Patent No. 4,806,524, IDS#A10 Paper No. 6), Hakimi *et al.* (European Publication No. 0510356 A1, IDS#B11 Paper No. 3) and Elliott *et al.* (WO 95/05465). The basis for this rejection is the same as that set forth in the corresponding rejection under 35 USC 103.

Art Unit: 1647

Claim 5 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-6 and 15 of U.S. Patent No. 6,025,324 in view of Kawaguchi *et al.* (US Patent No. 4,806,524, IDS#A10 Paper No. 6), Hakimi *et al.* (European Publication No. 0510356 A1, IDS#B11 Paper No. 3), Elliott *et al.* (WO 95/05465) and Garvin *et al.* US Patent No. 5,641,663. The basis for this rejection is the same as that set forth in the corresponding rejection under 35 USC 103.

Claims 30-48 and 55-60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-6 and 15 of U.S. Patent No. 6,025,324 in view of Kawaguchi *et al.* (US Patent No. 4,806,524, IDS#A10 Paper No. 6), Hakimi *et al.* (European Publication No. 0510356 A1, IDS#B11 Paper No. 3), Elliott *et al.* (WO 95/05465) and Burg *et al.* US Patent No. 6,340,742 B1. The basis for this rejection is the same as that set forth in the corresponding rejection under 35 USC 103.

### ***Conclusion***

No claims are allowed.

Art Unit: 1647

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on Mondays-Fridays 8:00 a.m. - 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

*RMD*

RMD

March 20, 2002

*Elizabeth C. Kemmerer*

ELIZABETH KEMMERER  
PRIMARY EXAMINER